EDITORIAL

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Pseudomyxoma Peritonei

A Cancer Whose Biology Is Characterized by a Redistribution Phenomenon

Gough and associates are to be congratulated on their valuable contribution to the literature of cancer surgery. Their scholarly and critical approach to this disease process has given us new and valuable information about an unusual problem. These authors have emphasized some clinical features of this disease that must be appreciated if proper management is to occur.

First, pseudomyxoma peritonei is a treatable disease process. Its unfamiliarity should not lead us to abandon therapeutic options even though no prospective randomized trials are available. Regional therapies can be effective. Repeated surgical procedures and regional intraperitoneal therapy can prolong the patient's survival. I agree with these authors that systemic chemotherapeutic treatments are often debilitating and rarely associated with prolonged survival with a good quality of life. Systemic chemotherapy is rarely indicated for this disease process, which is confined to the abdominal cavity. It should only be considered for patients who have no other options.

Early in this commentary, I feel compelled to comment that patient selection is of paramount importance in achieving beneficial results with peritoneal carcinomatosis. It cannot be emphasized too strongly that an aggressive surgical approach to extensive carcinomatosis from adenocarcinoma has high morbidity and mortality rates but affords little benefit in terms of long-term survival. This is in great contrast to the treatment for pseudomyxoma peritonei.

I compliment these authors on their attempt to dispel the myth that pseudomyxoma peritonei is a benign condition associated with long-term survival in a large proportion of patients. This is an aggressive disease process with no survival in patients followed long term without definitive treatment. In my opinion, this low-grade cancer requires management that uses a well-organized strategy as early as possible in the course of the disease.

The lack of a coherent state-of-the-art therapy for pseudomyxoma peritonei is apparent in this article. Uncertainty exists worldwide in regard to the optimal surgical management, and no definite recommendations for a surgical approach can be extracted from this article. Also, precise indications for regional therapies were not given, and the beneficial results of treatment were suggestive rather than definitive. This article presents an honest but scrambled list of indications for treatment and management options that represents our current state of ignorance in dealing with pseudomyxoma peritonei.

Perhaps, the major issue confounding optimal management concerns a failure to understand the natural history of pseudomyxoma peritonei. Can we clearly establish the clinical entity of pseudomyxoma peritonei? Is there a fundamental principle of tumor biology that this disease manifests that distinguishes it? I think that there is. Pseudomyxoma peritonei, whether it be of appendiceal, ovarian, or colorectal origin, is a disease process characterized by a redistribution phenomenon. Redistribution means that large volumes of tumor will be found at some predetermined anatomic sites within the peritoneal cavity but will be absent or in a greatly reduced volume at other sites. Pseudomyxoma peritonei will have large-volume cancer in the greater omentum ("omental cake"), at the undersurface of the right hemidiaphragm, in the pelvis, in the right retrohepatic space, in the left abdominal gutter, and at the ligament of Treitz. The peritoneal surfaces of the bowel are completely free of tumor; these surfaces are relentlessly moved by peristaltic activity. They are never extensively involved unless there have been multiple prior surgical procedures. For this unique pattern of cancer dissemination to occur, several biologic requirements and physiologic phenomena must be operating. Pseudomyxoma cells do not have adherence molecules exposed on the cell surface. This lack of "stickiness" means that the tumor cell will not actively attach to an abdominal or pelvic surface. The

tumor will progress by the production of mucus, exfoliation of tumor cells, and a redistribution of these cells around the abdomen, according to two physiologic mechanisms. First, the mucinous tumor cells will accumulate at the sites of peritoneal fluid reabsorption. Large pores present on the peritoneal surface of the omentum and the undersurface of the diaphragm are open lymphatic lacunae.[1] This is the anatomic site where peritoneal fluid is absorbed. Ascitic fluid that is drawn to these areas by intraperitoneal fluid dynamics leads to an accumulation of cancer cells beneath the right hemidiaphragm and within the greater omentum. Second, these cells will settle by gravity within the dependent portions of the abdomen (intra-abdominal "puddles"). This means the tumor will accumulate in large volumes within the pelvis, within the right retrohepatic space, in the left abdominal gutter, and at the ligament of Treitz (Fig. 1).

In summary, we define pseudomyxoma peritonei as a clinical entity characterized by (1) the presence of mucinous ascites from a grade I cystadenocarcinoma, (2) redistribution of the tumor within the abdominal cavity to predictable anatomic sites, and (3) an origin usually from the appendix or ovary.

With the new concept of this disease, I think that a new strategy for management has evolved. It does not include the use of repeated operations required over many years in an attempt to prolong survival. I favor a dose-intensive approach that combines maximal surgery and maximal regional intraperitoneal chemotherapy. The surgery includes a series of well-defined peritonectomy procedures that can strip all disease from the parietal peritoneal surfaces and resect all visceral peritoneal surfaces that are involved. This leaves the abdomen visibly disease free.[2] In the early postoperative period, before adhesions form and tumor cells become entrapped within fibrinous accumulations, intra-abdominal irrigation and chemotherapy are used to destroy the few remaining cancer cells.[3] Treatment failure, if it occurs, is usually associated with a nonuniform intraperitoneal chemotherapeutic distribution.

If surgery and chemotherapy are combined as a single dose-intensive event, reoperation is necessary in only 10% of patients. If it is required, subsequent surgical procedures are almost always associated with a reduction in the extent of intra-abdominal cancer. Without intraperitoneal chemotherapy, each reoperation becomes more difficult until eventually surgical treatment is impossible or its use is associated with very high morbidity and mortality rates.

Related to this, I disagree with these authors that the biology of pseudomyxoma peritonei changes over time with multiple reoperations. This is known to be true of intra-abdominal sarcoma. The areas of high-grade disease in a sarcoma tend to be those histologic types that recur. The surgical observation is that recurrent sarcoma is more invasive, more liable to metastasize distantly, and more difficult to resect curatively at each subsequent reoperation. Pseudomyxoma is different. The change that occurs with pseudomyxoma peritonei is a result of cancer regrowth in scar tissue. The pseudomyxoma cells become entrapped in fibrinous material, grow out in scar tissue, and with repeated operations, become intimately involved with the visceral peritoneum. This means that each reoperation is associated with a more difficult dissection with higher postoperative morbidity and mortality rates. For this reason, I advocate complete cytoreduction with the use of the required peritonectomy procedures followed by early postoperative intraperitoneal chemotherapy in all patients. Early dose-intensive treat-

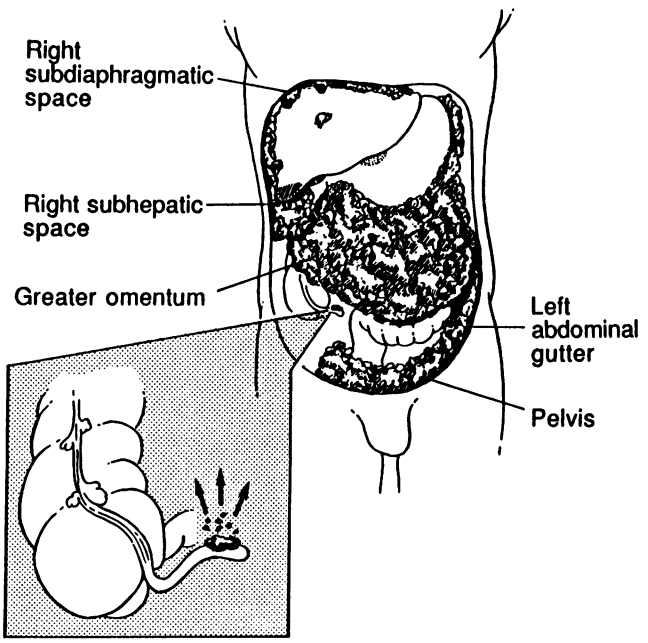

Figure 1. Redistribution of peritoneal carcinomatosis from pseudomyxoma peritonei. Grade I mucinous cancer arising from the appendix as a villous adenoma bursts through the thin wall of the appendix. It spreads widely throughout the peritoneal cavity but does not invade past the peritoneal surface; it progresses exuberantly on the surface. With extensive mucus production, it continues to exfoliate tumor cells widely into the free peritoneal cavity. These grade I tumor cells rarely metastasize through the lymph channels or by hematogenous routes. Similarly, their cell surfaces do not have the adhesion molecules to stick randomly to peritoneal surfaces. Therefore, the clinical feature that most distinctly characterizes pseudomyxoma peritonei is its tendency to "redistribute" around the peritoneal cavity. Portions of the peritoneum that are in motion, such as visceral peritoneum on the bowel surface, are only sparsely seeded by the intra-abdominal disease spread. The abdominal surfaces that absorb peritoneal fluid, such as the greater omentum and undersurface of diaphragms, are coated by large numbers of tumor cells as fluid is concentrated during months and years. The other mechanism of tumor redistribution is simply gravity. Free-floating intraperitoneal tumor cells will puddle in large volumes within the pelvis, within the right subhepatic space, within the left abdominal gutter, and at the ligament of Treitz.

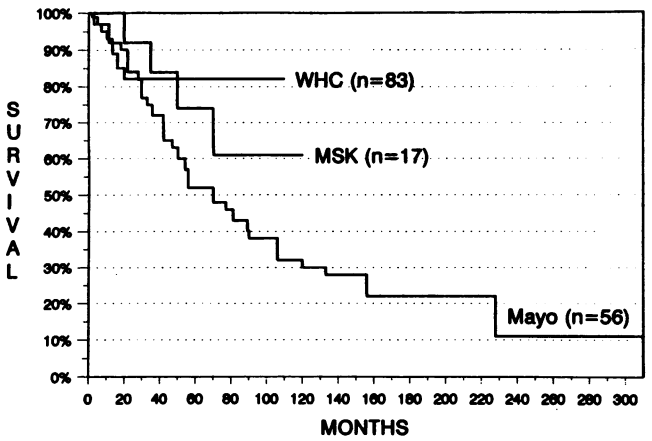

Figure 2. Overall survival rates of patients with pseudomyxoma peritonei. Survival curves modified from the experience with pseudomyxoma peritonei from the Washington Hospital Center (WHC), Memorial Sloan-Kettering Cancer Center (MSK), and the Mayo Clinic (Mayo). The WHC experience involves a treatment using peritonectomy procedures as required and early postoperative intraperitoneal chemotherapy. The MSK experience involves repeated surgical procedures and systemic chemotherapy. The Mayo experience involves repeated surgical procedures and intraperitoneal radioisotopes or chemotherapy.

ment of this malignancy, as in all cancers, will have the highest probability for cure with the lowest morbidity and mortality rates.

Studies of pseudomyxoma peritonei bring this disease process into a new focus. This is a nonmetastasizing cancer with a devastating outcome because of local progression if therapy is not definitive early on. These patients should be treated for cure. This disease does not need to follow "an unremitting but prolonged clinical course."[4] Using the cytoreductive approach, this disease can and should be cured in a majority of patients. The survival rates of patients with pseudomyxoma who were treated at the Washington Hospital Center, Memorial Sloan-Kettering Cancer Center, and the Mayo Clinic are shown in Figure 2.[4–6] These groups of patients may not be completely the same, and further follow-up is indicated. There is a suggestion that the cytoreductive approach to pseudomyxoma peritonei may be the most effective.

Paul H. Sugarbaker, M.D.
Washington, D.C.

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